specification (page 8, lines 1 and 8-13) as it teaches the use of either avidin or streptavidin in the compositions and practices of the invention. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made." No new matter is believed added.

I. Rejection under 35 U.S.C. § 112, first paragraph

Claims 1-2 and 15-16 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one of skill in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action indicates that the rejection is maintained for reasons of record in the previous Office Action (Paper No. 11). Further, the Examiner characterizes the Applicant's response as stating that: 1) teachings incorporated by reference in the instant specification provide sufficient description of receptor/ligand pairs and methods of conjugating different biomolecules to describe the broad genus of methods encompassed by the claims; 2) the state of the art at the time of the invention was sufficiently developed to allow one of skill in the art to envision a sufficient number of different embodiments of the claimed invention to describe a broad genus; 3) the specification is enabling in view of the prior art and teachings of the specification.

With regard to assertions directed to enablement of the claimed invention, the Examiner has noted that as the instant rejection was for lack of description in the specification such that one of skill in the art would not recognize that applicants were in possession of the claimed invention, arguments raised by the Applicants' regarding enablement were not relevant to the instant rejection.

Briefly, Applicants respectfully disagree with the Examiner's position that the arguments relating to enablement were irrelevant. While it is true that written description and enablement are separate requirements for patentability, it is not true that issues related to enablement do not impact

the issue of written description. The recognition that enablement is relevant when considering whether an application fulfills the written description description is evidenced in the guidelines promulgated by the PTO itself. Specifically, as shown on page 1106 of the "Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112, paragraph 1" (Federal Register Vol. 66, No. 4), the list of factors to be considered when a determination of whether the requirement for adequate written description is met includes consideration of the level of skill and knowledge in the art and the method of making the claimed invention. Specifically, it states in part:

> [f]actors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

Consistent with these guidelines, information relating to how or whether certain embodiments of the invention could be made given the teaching of the specification and the knowledge of those of skill in the art are necessarily relevant to proper consideration of whether a specification fulfills the written description requirement. Applicants therefore request that the Examiner properly reconsider all the submitted evidence in regard to the written description requirement including that which the Examiner characterizes as relating to enablement.

In regard to the present invention, the Examiner has stated that there are at least three essential elements of the Applicant's invention for delivery of active biomolecules to a cell: 1) identification of "ligand"/"receptor" pairs suitable for use in the claimed invention; 2) covalent attachment of the "receptor" to the surface of the cell; and 3) complexing the desired biomolecule with the ligand.

Without necessarily agreeing with the Examiner that this is an accurate categorization, Applicants do submit that if this were the case, the present invention as claimed falls well within the category of an invention that meets the written description requirement and that the invention would be reasonably conveyed to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. However, as is noted in the Office Action, the Examiner is not yet convinced. Applicants suggest that this is due to the Examiner not considering the application as filed and the cited references, evidencing the state of the art at the time the application was filed, in the manner that one of skill in the relevant art would consider them. However, Applicants do note and appreciate that the Examiner does not contest that the 3rd essential element, namely, the act of complexing the desired biomolecule with a ligand.

Specifically, it is alleged by the Examiner that each of the submitted references directed toward the characterization of receptor/ligand pairs does so in the context of natural receptors. Further, it is alleged that the concept of designing ligands such that one can interfere with the infection process does not adequately address the issue of covalently attaching a biomolecule to a cell surface to generate a receptor. Further, it is alleged that each of the references submitted that are directed toward methods of conjugating different biomolecules are directed towards doing so in free solution. Apparently for this reason, the Examiner adopts the position that none of the teachings appear to be directed towards conjugation of a biomolecule to the surface of a cell. Further, the Examiner indicates that it is unclear whether any of the methods disclosed in the references for biomolecules other than biotin or avidin would be compatible with cell survival. (Applicants note that the Examiner's use of the term biomolecule in regard to the molecule of the invention that is covalently attached to the cell surface is incorrect. The entity covalently attached to the surface of a cell is a "molecule." Applicants' use of the term "biomolecule" in this context is only for the sake of clearly avoiding any mischaracterization of the Examiner's comments in the Office Action and does not imply agreement of the Applicants with the Examiner's comments.)

Confusion of the use of the term "biomolecule" aside, in response to the Examiner's characterization of the references, Applicants' submit the that the alleged failure of each of the cited references to provide every detail of different aspects of the invention when viewed in isolation is neither relevant nor surprising. The present invention is novel over the prior art. As such, it is not possible for any single reference to provide each and every aspect, such as those examples touched on by the Examiner, as described above, without necessarily anticipating the invention. Such a standard is clearly improper and Applicants request reconsideration.

Rather, what is shown by the cited references is the high level of skill in the art regarding processes and steps that can be taken to provide the present invention and that one of skill in the art, recognizing clearly the many different ways of accomplishing and using the invention using the common knowledge of the art, of which the references provided are but a part, would recognize that the Applicants' had possession of the invention as claimed at the time of filing. More specifically, for example, references referred to by the Examiner as showing receptor-ligand pairs, but only in the context of natural receptor, put in possession of the skilled person many examples of the types of interacting species that can be used in the present invention. The concept of designing ligands that can interfere with the infection process illustrates, necessarily, that ligands can be designed to interact with specified receptors. Thus, it is clear that one of skill in the art would recognize not only the types or characteristics of interacting partners that could be used, but further, that artificial ligands could be designed as well.

In respect to the Examiner's arguments that the references provided did not properly address the issue of covalently attaching a biomolecule to a cell surface to generate a receptor, the Examiner acknowledges that other references provided do indeed provide teach methods of conjugating different biomolecules (Office Action; page 4, lines 3-5).

Furthermore, the Applicants submit that the skill of those in the art includes the knowledge of what types of cross-linking chemistries are compatible with cell survival and/or the level of experimentation required to determine whether a specific set of conditions provide an adequate number of surviving cells. However, even if one were to accept that only the type of chemistry used in the examples where biotinylation was used were to be compatible with cell survival, limitation of the invention to the use of biotin as a cell surface receptor is still clearly improper. The chemistry used to covalently attach biotin to the cell surface, specifically the use of NHS (N-hydroxysuccinimide ester) - based chemistry, can be and has been used to covalently cross-link many different types of molecules so long as they contain primary amines (see Attachment A). Using, for example, bifunctional NHS cross-linkers such as those described in Exhibit A, any two molecules containing primary amines can be cross-linked using the same chemistry used for biotinylation in the Examples. Thus, not only biotin, but also any other receptor molecule that contains a primary amine is suitable for attachment to the cell surface using the same chemistry as is described in the examples. Among these other well-recognized other receptor molecules with primary amine groups are peptides and proteins, modified nucleic acids and sugars. Further, as the conditions and chemistry used to form the cross-links in each of these cases would be identical, or virtually identical, to that used for the biotinylation of a cell surface, Applicants submit that the Examiner's allegation that only biotinylation of the cell surface is clearly compatible with cell survival is incorrect and is not based on scientific evidence. One of skill in the art would clearly recognize that virtually any molecule containing and/or capable of being modified to contain a primary amine could be attached to the surface of a cell using reagents routinely used in the relevant art and utilizing the same type of reagents and chemistry that were used in the examples of the present application.

Thus, while the Examiner specifically characterizes each of these sets of references, in turn, as falling short of providing evidence of the high level of skill in the art, the Examiner can apparently only do so when these references are not considered as part of the whole knowledge of one of skill in the art. Specifically, the Examiner objects that one set of references only pertains to natural

ligand-receptor pairs. However, the second set of references teaches the design of non-naturally occurring ligands. But then, the Examiner objects that the second set of references doesn't teach covalent attachment of a receptor to a cell surface. However, the third set of references referred to by the Examiner does teach the conjugation of different molecules, including what the Examiner has termed biomolecules. To this, the Examiner objects that the methods taught are directed towards doing so in free solution and that it is unclear whether the methods disclosed in the references for receptors (stated by Examiner as biomolecules) other than biotin or avidin would be compatible with cell survival. However, the methods used for attaching avidin to the surface of a cell so as to provide a receptor utilize conditions and chemistries highly suitable for the attachment of peptides and proteins, modified nucleic acids, sugars and any other molecule having primary amine functionalities. Clearly, one of skill in the art would recognize that the Applicants' had possession of the invention at the time the application was filed.

Furthermore, in regard to the viability of cells modified to bear cell surface receptors, whether or not one of skill in the art knew that a particular type of cross-linking chemistry would necessarily result in viable cells is not required in order for that person of skill in the art to recognize that the inventors had possession of the claimed invention. Indeed, the invention as claimed does not require that the cells survive and/or be capable of reproducing following the covalent attachment of the receptor.

In summary, the application as filed provides explicit teaching as to what was the invention and fulfills the written description requirement for the invention as claimed. Essential elements, as defined by the Examiner, were recognized by the Examiner and listed in the Office Action. These include identification of ligand-receptor pairs, covalent attachment of the receptor to the cell surface and complexing the desired biomolecule with the ligand. Applicants submit that each of these are described in adequate detail for one of skill in the art to recognize that the Applicants had possession of the claimed invention. While the Examiner has argued that the supplied references only provide

general outline of how receptor/ligand pairs interact and for how to covalently conjugate different biomolecules, Applicants submit that these teachings are more than adequate, not only for those of skill in the art to recognize that the Applicants had possession of the invention as claimed, but also for enablement of innumerable examples of the invention. Further, Applicants submit that the many examples of the invention that would necessarily be recognized by those of skill in the art to fall within the scope of what the inventors considered their invention is an adequate number of species to support the broader genus described in claims 1 and 15.

For the reasons cited above, i.e., that the level of skill in the art is relatively high and includes: an understanding of the many different ligand / receptor pairs that can be used; how to generate fragments or variants of binding pairs that are functional; how to attach receptors to the surface of a cell, particularly any receptor containing a primary amine group, such as a peptide or protein; and that such modification of cells to include receptors would be compatible with cell survival; Applicants submit that one of skill in the recognize that one of skill in the art would have reasonably concluded that the Applicants were in possession of the claimed invention. Correspondingly, Applicants request removal of this basis of rejection for claims 1-2 and 15-16.

Applicants acknowledge Examiner's conclusion that claims 3, 7, 17 and 18 would be allowable if rewritten as independent claims comprising the limitations of the claims upon which they depended. Applicants have so rewritten said claims as claims 19, 7, 20 and 21 respectively.

Pursuant to the above remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of the application to issue.

Credit Card Payment Form PTO-2038 in the amount of $1310.00 and a Request for a Three Month Extension of Time are enclosed. Fees include $920 for Extension of Time, $54 for three (3)

claims in excess of twenty (20), and $336 for four (4) independent claims in excess of three (3). This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: BOX AF, Commissioner for Patents, Washington, D.C. 20231, on the date shown below.

Gwendolyn D. Spratt — 5-28-02

Gwendolyn D. Spratt — Date

JUN 0 6 2002
PATENT & TRADEMARK OFFICE

Version with Markings to Show Changes Made

In the claims:

7. (Twice amended) The method of claim 1, wherein the biologically active molecule is a nucleic acid, the ligand is PEI conjugated to avidin or streptavidin and the surface receptor is biotin.